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Synthesis of 4-Ethyloctahydroindolo[2,3-*a*]quinolizine-2-carbaldehydes

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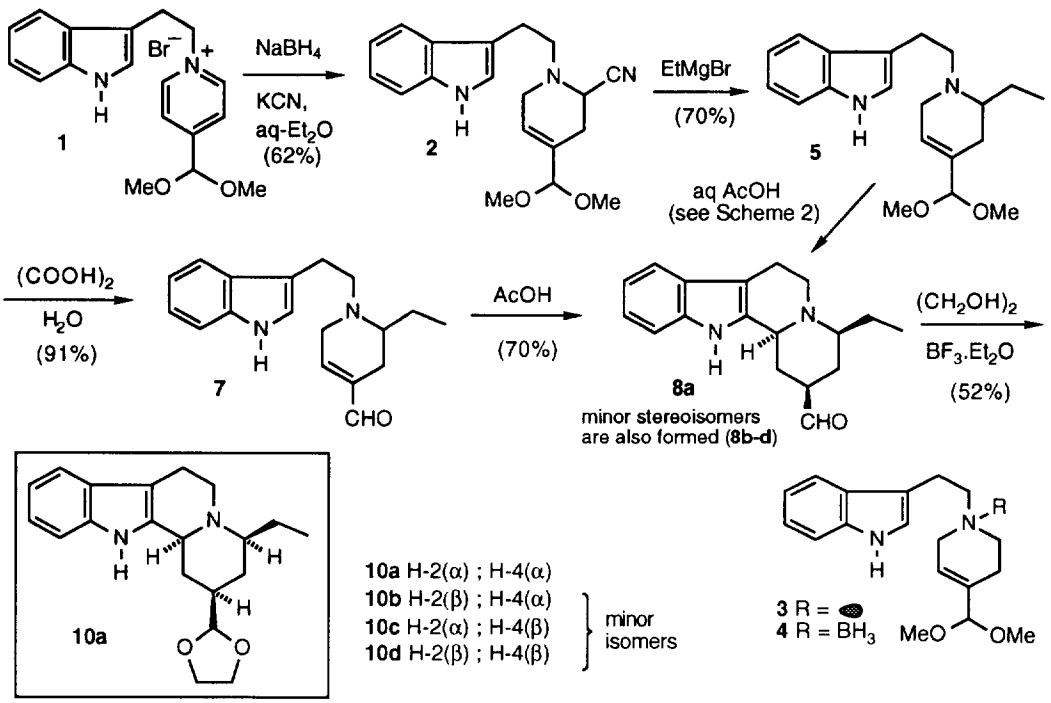
Abstract: The isomerization-cyclization of tetrahydropyridine **7** by AcOH leads to 4-ethyloctahydroindolo[2,3-*a*]quinolizine-2-carbaldehydes (**8**). When the process is carried out with aqueous AcOH, indolizidinoindole **9** is formed as a by-product in a competitive way. Compound **7** is available via reductive cyanation of pyridinium salt **1** followed by treatment of nitrile **2** with ethylmagnesium bromide. © 1997 Elsevier Science Ltd.

We have recently reported[1] the synthesis of indole alkaloid deethylibophyllidine using a *crisscross* approach in order to construct the pyrrolizino[1,7-*cd*]carbazole skeleton. After achieving this success, we became interested in developing the synthesis of more complex alkaloids with this skeletal-type using the same strategy. With this goal, we needed to develop a route to 2,4-disubstituted octahydroindolo[2,3-*a*]quinolizines. While many procedures have been described for the synthesis of 1,2-, 1,3- or 2,3-disubstituted octahydroindolo[2,3-*a*]quinolizines, due to the existence of many indole alkaloids with this pattern of substitution,[2] there is only one precedent for the synthesis of 2,4-disubstituted derivatives of this tetracyclic ring system.[3]

In this paper, we describe the synthesis of 4-ethyloctahydroindolo[2,3-a]quinolizine-2-carbaldehydes, by a procedure that could be extended to several 4-alkyl derivatives. The synthesis starts from the pyridinium salt **1**, obtained in quantitative form by reaction of tryptophyl bromide and the dimethyl acetal of 4-formylpyridine. The reductive cyanation[4] of **1** by means of sodium borohydride in the presence of an excess of cyanide ion gave 2-cyanotetrahydropyridine **2** in 62% yield. Tetrahydropyridine **3** and its amino-borane adduct **4** were also isolated as minor by-products. The introduction of the ethyl side chain was accomplished taking advantage of the behavior of α-aminonitriles that undergo substitution reactions upon treatment with Grignard reagents[5] instead of the addition observed when using organolithium derivatives.[6] Thus, cyanopiperideine **2** was converted to ethyltetrahydropyridine **5** in 70% yield by treatment with ethylmagnesium bromide (Scheme 1).[7]

The cyclization of tetrahydropyridines with an electron-withdrawing group upon the indole nucleus by means of isomerization of the double bond to the enamine, its protonation and finally, cyclization of the generated iminium salt, was described some years ago by Joule.[8] When we attempted the cyclization of acetal **5** in aqueous acetic acid (rfx, 16 h), in order to generate *in situ* the required aldehyde **7** and to promote the isomerization step, an unexpected indolizidinoindole **9** was obtained with the desired indoloquinolizine **8** (Scheme 2).[9]

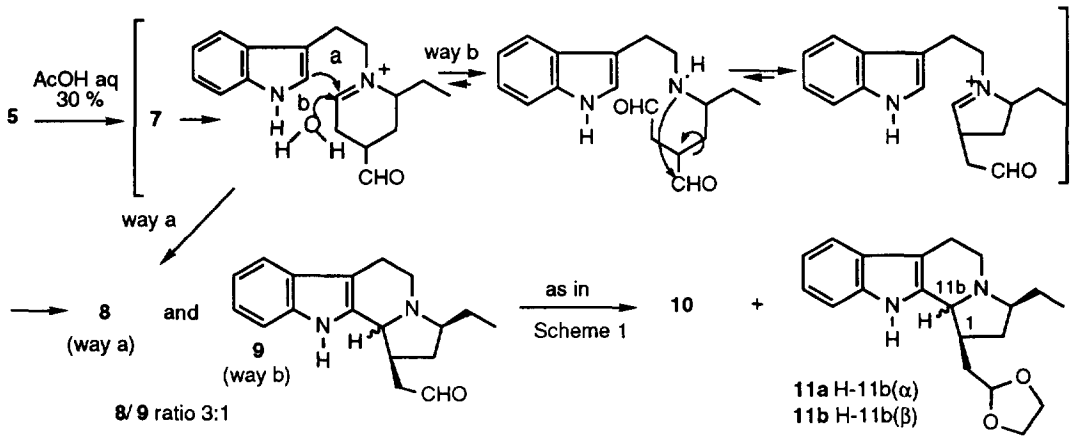


Scheme 1

GC-MS analysis of the reaction mixture was effected after protection of the crude aldehydes, **8** and **9**, as their corresponding ethylene acetals. Six acetals could be observed: four of the indoloquinolizine type **10** (**a**,**b**,**c**,**d**) in a 15:2:1:2 ratio, respectively, and two indolizinoindoles **11** (**a**,**b**) in a 4:2.5 ratio. Thus, the unexpected compound **11** was formed in a 1:3 ratio with the desired targets **10**. The formation of indolizidinoindoles **9** can be accounted for by hydrolysis of the intermediate iminium salt which generates a dialdehyde that evolves as depicted in Scheme 2. The most significant signals for compounds **11** are the triplets in ^{1}H NMR spectra at δ 5.07 (J= 6 Hz) and δ 5.15 (J= 5.5 Hz) corresponding to acetal methine in **11a** and **11b** respectively, which differ from indolo-quinolizidines **10** in which the multiplicity is a doublet, this acetal proton appearing at δ 4.6 for **10a** and δ 5.2 in **10b**.

In order to avoid the unwanted side products formed when the cyclization step was performed in an aqueous acid medium, the acetal **5** was hydrolyzed (oxalic acid aqueous)[10] prior to the cyclization step (Scheme 1). Treatment of the resulting α,β-unsaturated aldehyde **7** with glacial acetic acid (rfx, 45 min) allowed us to obtain only indoloquinolizine compounds **8**, which after acetalization furnished a mixture of four stereoisomers **10a**, **10b**, **10c**, **10d** in a ratio of 10:2:1:2, respectively. In this case, the ratio of *all-cis* isomer **10a** with respect to other isomers (2:1) compared with the (3:1) ratio observed in the aqueous series, can be attributed to the short reaction time in the anhydrous version, which might reflect a non thermodynamic process. It is well-known that in kinetically-controlled processes, trans isomers (relationship between C-2 and C-12b) are prefered whereas under thermodynamic control cis isomers prevail.[11]

Octahydroindolo[2,3-*a*]quinolizines **10** may exist in three conformations (T, C1, C2) as in compounds embodying the quinolizidine ring system.[12] Indoloquinolizidine **10a**, which was formed as the major isomer



Scheme 2

(80%) shows the most stable configuration and conformation: a T conformation in which the two substituents at C-2 and C-4 are located equatorially (see Figure 1). The ^{13}C NMR shift of C-7 (δ 21.9) is diagnostic of the conformation, whereas the chemical shifts of C-2, C-4, and C-12b are significant for the relative configuration.[13] Taking this major isomer as a model, the minor isomers **10b** and **10c** are assigned as the epimers at C-2 and C-4 respectively. In both compounds the preferred conformation also has a trans relationship between the C and D rings. In contrast, isomer **10d** shows a cis (C2) conformation in the subunit of quinolizidine, giving an equatorial disposition for substituents at C-2 and C-4. The signal at δ 16.7 for C-7 is a diagnostic value for a cis conformation between the C and D rings.[13] Another significant signal for **10d** appears in the ^1H NMR spectrum in which H-12b resonates at δ 4.2 as a broad signal.[14] Compounds with the acetal in equatorial disposition show the methine proton at δ 4.6, whereas in the isomer **10b**, with this substituent in axial position, it resonates at δ 5.2.

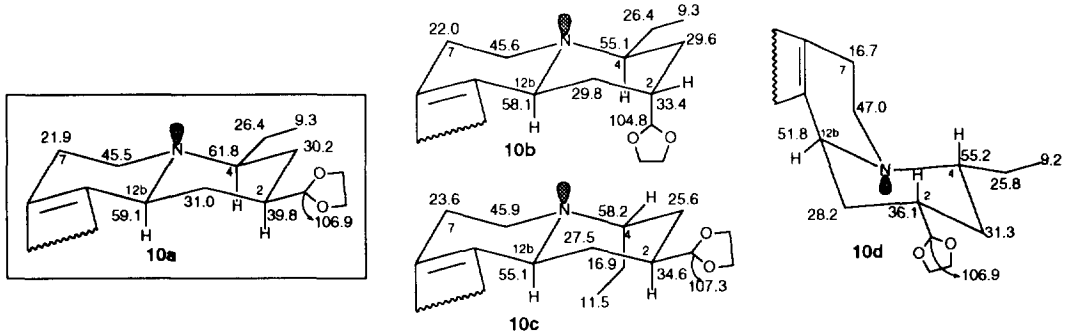


Figure 1. Spectroscopic Analysis of Tetracyclic Compounds 10

In summary, the synthesis of 4-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-2-carbaldehyde (**8**) has been achieved in a four synthetic step sequence. This procedure may allow the synthesis of several 2,4-disubstituted derivatives with this indoloquinolizine pattern, by modifying on the oxidation level of the aldehyde and/ or the Grignard reagent used.

EXPERIMENTAL

General. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 MHz and 50.3 MHz. In addition, 2D NMR COSY and HMQC experiments were performed on a Varian XL-500 instrument. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Infrarred spectra were recorded on a Nicolet 205 FT-IR spectrophotometer, and only noteworthy absorptions (cm^{-1}) are listed. Mass spectra were determined on a Hewlett-Packard 5988 A mass spectrometer or on a Autospec-VG (HRMS). TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located by UV light and a 1% $KMnO_4$ solution or hexachloroplatinate reagent. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh). All reactions were carried out under an argon or nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Melting points were determined in a capillary tube on a Büchi apparatus. Microanalyses were performed by the "Centro de Investigación y Desarrollo" (CSIC), Barcelona.

4-(Dimethoxy)methylpyridine.[15] Trimethyl orthoformate (61 ml, 560 mmol) was added to a solution of 4-pyridinecarbaldehyde (20 g, 190 mmol) in methanol saturated with HCl (37 ml). The solution was heated at reflux for 6 h and then cooled, neutralized with 30% methanolic KOH, and filtered. The filtrate was distilled and 4-dimethoxymethylpyridine (23.5 g, 83%) was collected: bp 71-72 °C/3-4 mm Hg; TLC R_f = 0.45 (hexane:EtOAc 2:1); IR (neat) 1602; ^1H NMR 3.33 (s, 6H, OCH_3), 5.4 (s, 1H, OCHO), 7.37 (dd, *J*= 6, 2.5 Hz, 2H, H-3 and H-5), 8.63 (dd, *J*= 6, 2.5 Hz, 2H, H-2 and H-6); ^{13}C NMR 52.7 (OMe), 101.2 (OCHO), 121.8 (C-3 and C-5), 146.2 (C-4), 150.0 (C-2 and C-6). Anal. Calcd for $C_8H_{11}NO_2 \cdot 1/2H_2O$: C, 59.25; H, 7.40; N, 8.84. Found: C, 59.25; H, 7.04; N, 8.64.

4-(Dimethoxy)methyl-1-[2-(3-indolyl)ethyl]pyridinium Bromide (1). A mixture of tryptophyl bromide[16] (13.6 g, 65 mmol) and 4-dimethoxymethylpyridine (9.9 g, 65 mmol) was stirred at 80-95 °C for 16 h. Pyridinium salt **1** (22.7 g, quantitative) was obtained as a gummy solid, which was used without further purification: ^1H NMR (CD_3OD) 3.32 (s, 6H, OCH_3), 3.47 (t, *J*= 6.3 Hz, 2H, CH_2), 4.91 (t, *J*= 6.3 Hz, 2H, CH_2N^+), 5.52 (s, 1H, OCHO), 6.97 (t, *J*= 6.5 Hz, 2H, H-5' and H-6'), 6.98 (s, 1H, H-2'), 7.3 (d, *J*= 6.5 Hz, 2H, H-4' and H-7'), 7.88 (d, *J*= 6.5 Hz, 2H, H-3 and H-5), 8.62 (d, *J*=6.5 Hz, 2H, H-2 and H-6).

4-(Dimethoxy)methyl-1-[2-(3-indolyl)ethyl]-1,2,3,6-tetrahydropyridine-2-carbonitrile (2). Hydrochloric acid (6 N, 34 ml) was added dropwise to a stirred solution of sodium cyanide (25.6 g, 390 mmol) in water (40 ml), layered with ether (100 ml), and kept below 0 °C. To the resulting mixture was added a solution of pyridinium bromide **1** (22.7 g, 65 mmol) in MeOH (34 ml) and then sodium borohydride (3.1 g, 82 mmol) portionwise. The mixture was stirred at room temperature for 16 h, the ether was decanted, and the aqueous layer was extracted with ether (2 x 100ml). The ethereal extracts were washed with brine, dried, and evaporated. The residue was purified by chromatography. On elution with hexane-CH_2Cl_2 (1:1), a mixture of aminoborane aduct **4** and nitrile **2** (7.5 g) was isolated in a 1:5 ratio, respectively. [Both compounds were separated by additional chromatography (hexane-CH_2Cl_2, increasing polarity) Aminoborane **4** was converted to amine **3** by heating at reflux in ethanol]. Further elution with CH_2Cl_2 gave, in addition, 6.66 g (62% overall yield) of **2**. Final elution (EtOAc) gave 919 mg (5%) of **4-(dimethoxy)methyl-1-[2-(3-indolyl)ethyl]-1,2,3,6-tetrahydropyridine (3)**.In some runs, fractions with a mixture of **2** and **3** were eluted. Both compounds were separated by an extractive process with an aqueous solution of pH 3.5 (AcOH/NaOAc) and CH_2Cl_2, taking advantage of the low basicity of **2**.

For **2**: TLC R_f = 0.70 (EtOAc:CH_2Cl_2 2:3); IR (neat) 3409, 2222, 1621; ^1H NMR 2.35 (d, *J*=17.5 Hz, 1H, H-3_{ax}), 2.60 (dm, *J*=17.5 Hz, 1H, H-3_{eq}), 3.08 (dm, *J*=16 Hz, 1H, H-6_{ax}), 2.8-3.0 (m, 4H, CH_2), 3.31 and 3.33 (2 s, 3H each, OCH_3), 3.52 (dm, *J*=16 Hz, 1H, H-6_{eq}), 4.03 (dd, *J*=6, 2 Hz, 1H, H-2), 4.62 (s, 1H, OCHO), 5.93 (t, *J*=4 Hz, 1H, H-5), 7.02 (d, *J*=2 Hz, 1H, H-2'), 7.16 (td, *J*=7, 1 Hz, H-6'), 7.20 (td, *J*=7, 1 Hz, H-5'), 7.35 (d, *J* =7 Hz, H-7'), 7.59 (d, *J* =7 Hz, H-4'), 8.10 (brs, NH); ^{13}C NMR 23.1 (CH_2), 28.2 (C-3), 48.3 (C-6), 49.5 (C-2), 53.1 and 53.2 (OCH_3), 56.0 (NCH_2), 104.0

(OCHO), 111.2 (C-7'), 113.3 (C-3'), 116.6 (CN), 119.3 (C-5'), 121.6 and 122.0 (C-2' and C-6'), 123.8 (C-5), 127.2 (C-3a), 129.8 (C-4), 136.1 (C-7a); MS(EI) *m/z* (%) 325 (M^+,<1), 195 (18), 167 (16), 144 (88), 75 (100). Anal. Calcd for $C_{19}H_{23}N_3O_2 \cdot 5\ H_2O$: C, 68.26; H, 7.18; N, 12.57. Found: C, 68.27; H, 6.94; N,12.02.

For **3**: TLC (Al_2O_3) R_f = 0.70 (EtOAc); IR (neat) 3410, 1650; ^{1}H NMR 2.22 (brs, 2H), 2.6-3.5 (m, 8H), 3.32 (s, 6H, OCH_3), 4.60 (s, 1H, OCHO), 5.90 (brs, 1H, H-3), 7.0 (td, *J* = 7.5, 1 Hz, H-6), 7.1 (d, *J*= 2 Hz, 1H, H-2), 7.2 (td, *J* = 7.5, 1 Hz, 1H, H-5), 7.35 (d, *J* = 7.5Hz, 1H, H-7), 7.59 (d, *J* = 7.5 Hz, 1H, H-4), 8.20 (brs, 1H, NH); ^{13}C NMR 22.8 (CH_2), 24.5 (C-5), 49.6 (C-6), 51.9 (C-2), 53.1 (OCH_3), 58.8 (NCH_2), 104.8 (OCHO), 111.0 (C-7), 113.4 (C-3'), 118.4 (C-4'), 118.7 (C-5'), 121.4 and 121.6 (C-2' and C-6'), 123.6 (C-3), 127.2 (C-3a), 132.9 (C-4), 136.1 (C-7a). MS (EI) *m/z* (%) 300 (M^+,<1), 268 (12), 170 (100), 130 (64), 75 (36). Anal. Calcd for $C_{18}H_{24}N_2O_2 \cdot H_2CO_3$: C, 62.98; H, 7.18; N, 7.73. Found: C, 62.52, H, 7.11; N, 8.17.

For **4**: TLC R_f = 0.80 (EtOAc:CH_2Cl_2 2:3); IR (neat) 3410, 2367, 1630; ^{1}H-NMR 2.30 (brs, 2H), 2.9-3.4 (m, 6H), 3.30 (s, 6H, OCH_3), 3.6-3.7 (m, 2H), 4.62 (s, 1H, OCHO), 5.8 (brs, 1H, H-3), 7.02 (d, *J*=2 Hz, 1H, H-2), 7.12 (td, *J* =7.5, 1 Hz, 1H, H-6), 7.20 (td, *J*=7.5, 1 Hz, 1H, H-5), 7.37 (d, *J*=7.5, 1 Hz, 1H, H-7), 7.63 (d, *J* =7.5 Hz, 1H, H-4), 8.06 (brs, NH); ^{13}C NMR 20.1 (CH_2), 20.3 (C-5), 53.3 (OCH_3), 53.6 (C-6), 57.1 (C-2), 59.3 (NCH_2), 104.0 (OCHO), 111.2 (C-7), 112.3 (C-3'), 118.6 (C-4'), 119.5 (C-5'), 119.9 (C-6'), 112.0 (C-2'), 122.2 (C-3), 127.0 (C-3a), 132.8 (C-4), 136.2 (C-7a); MS(EI) *m/z* (%) 314 (M^+, <1), 268 (10), 170 (100), 154 (16), 144 (16), 140 (33), 138 (25)

2-Ethyl-4-(dimethoxy)methyl-1-[2-(3-indolyl)ethyl]-1,2,3,6-tetrahydropyridine (5). Ethylmagnesium bromide (1 M in THF, 6.4 ml) was added dropwise to a cooled (0 °C) solution of amino nitrile **2** (0.7 g, 2.15 mmol) in THF (7 ml). The resulting mixture was stirred for 5 h at room temperature. After quenching with EtOAc, water was added and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried and concentrated. The residue was chromatographed. On elution with CH_2Cl_2, some starting α-aminonitrile (100 mg) was recovered. Further elution (CH_2Cl_2/EtOAc 1:1) gave a minor amount of 2-ethyl-4-(dimethoxy)methyl-1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydro-pyridine (**6**).[7] Further elution (EtOAc) gave **5** (485 mg, 70%; 82% based upon recovered starting **2**) as a clear oil: TLC R_f = 0.20 (EtOAc:CH_2Cl_2 2:3); IR (neat) 3413, 1648; ^{1}H NMR (COSY) 0.87 (t, *J* =7.5 Hz, CH_3), 1.31 (ddq, *J* =13, 9, 7.5 Hz, 1H, C*H*$_2$CH$_3$), 1.59 (ddq, *J* =13, 4.5, 7.5 Hz, 1H, C*H*$_2$CH$_3$), 1.90 (ddd, *J* =17.5, 4.5, 1.5, 1H. 3-H), 2.14 (ddd, *J* =17.5, 4.5, 2 Hz, 1H, 3-H), 2.73 (dddd, *J* =9, 4.5, 4.5, 4.5 Hz, 1H, H-2$_{eq}$), 2.79 and 2.83 (2dt *J* =10, 6 Hz each, 2H, InCH$_2$), 2.91 and 2.93 (2td , *J* =13.5, 6 Hz each, 2H, NCH_2), 3.28 and 3.30 (2s, 3H each, OCH_3), 3.33 (d. *J* =1.5 Hz, 2H, H-6), 4.54 (s, 1H, OCHO), 5.78 (d, *J* =1.5 Hz, 1H, H-5), 6.97 (s, 1H, H-2'), 7.05 (t, *J*=7 Hz, 1H, H-6'), 7.12 (t, *J*=7 Hz, 1H, H-5'), 7.29 (d *J* =7 Hz, 1H, H-7'), 7.54 (d, *J* =7.5 Hz, 1H, H-4'), 7.95 (brs, NH); ^{13}C NMR (HMQC): 11.0 (CH_3), 21.9 (CH_2), 23.6 (CH_2In), 26.2 (C-3), 48.8 (C-6), 53.0 (NCH_2), 53.2 (OCH_3), 57.7 (C-2), 105.2 (OCHO), 111.1 (C-7'), 114.5 (C-3'), 118.8 (C-4'), 119.1 (C-5'), 121.6 (C-2'), 121.8 (C-6'), 123.5 (C-5), 127.5 (C-3a), 132.2 (C-4), 136.2 (C-7a); MS(EI) *m/z* (%) 329 (M+1,45), 328 (M^+,12), 357 (M+29,7), 369 (M+41,1), 297 (100). Anal. Calcd for $C_{20}H_{28}N_2O_2.H_2O$: C, 69.20, H, 8.67, N, 8.08. Found: C, 68.90, H, 8.27, N, 8.40. HRMS $C_{20}H_{28}N_2O_2$ 328.2151, found 328.2155

2-Ethyl-1-[2-(3-indolyl)ethyl]-1,2,3,6-tetrahydropyridine-4-carbaldehyde (7). A solution of acetal **5** (1.95 g, 5.94 mmol) in 5% aqueous oxalic acid (50 ml) was stirred at room temperature for 30 min. After basification with aqueous Na_2CO_3 the mixture was extracted with CH_2Cl_2, and the combined organic extracts dried and concentrated to afford **7** (1.51 g, 91%) which was used without further purification: mp 81-83 °C; TLC R_f = 0.20 (EtOAc:CH_2Cl_2 2:3); IR (neat) 3313, 1677; ^{1}H NMR 0.92 (t, *J*=7.5 Hz, 3H, CH_3), 1.31 and 1.62 (2m, 1H each, CH_2), 2.25 (ddd, *J*=17.5, 5.5, 1.5 Hz, 1H, H-3$_{ax}$), 2.40 (ddd, *J*= 17.5, 4.5, 2 Hz, 1H, H-3$_{eq}$), 2.80-2.82 (m, 1H, H-2$_{eq}$), 2.83-2.91 (m, 2H, CH_2), 2.96-3.04 (m, 2H, NCH_2), 3.55 (brs, 2H, H-6), 6.80 (brs, 1H, H-5), 7.02 (d, *J*=2 Hz, 1H, H-2), 7.13 (td, *J*=7 Hz, 1H, H-6), 7.15 (td, *J*=7 Hz, 1H, H-5'), 7.35 (d, *J*=7 Hz, 1H, H-7), 7.60 (d, *J*=7 Hz, 1H, H-4), 8.30 (brs, 1H, NH) 9.50 (s, 1H, CHO); ^{13}C NMR (HMQC) 10.9 (CH_3), 21.2 (*C*H$_2$CH$_3$), 23.6 (CH_2), 24.2 (C-3), 49.5 (C-6), 53.2 (NCH_2), 57.0 (C-2), 111.2 (C-7), 114.0 (C-3), 118.6 (C-4'), 119.1 (C-5'), 121.5 (C-2), 121.8 (C-6), 127.3 (C-3a), 136.2 (C-7a), 138.7 (C-4), 147.7 (C-5).

(2*RS*,4*SR*,12b*SR*)-4-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-2-carbaldehyde (8). A solution of **7** (1.3 g, 4 mmol) in glacial AcOH (160 ml) was purged with Ar for 30 min, then heated at reflux (110 °C) for 45 min. The solution was evaporated and the residue was dissolved with CH_2Cl_2 and the mixture was basified with aqueous Na_2CO_3 in an ice bath. The organic layer was separated off, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50ml). The combined organic layers were washed with brine, dried and evaporated to give 1.2 g (89%) of crude aldehydes **8** as a black solid used for the next reaction without purification. An analytical sample for the major isomer **8a** was obtained by chromatohraphy (Florisil®, EtOAc): TLC (Al_2O_3) R_f = 0.70 (EtOAc-CH_2Cl_2 2:3); IR (neat) 3400, 1718; ^1H NMR 0.99 (t, *J*=7.5 Hz, 3H, CH_3), 1.50 (q, *J*=12 Hz, 1H, H-1_{ax}), 1.63 (q, *J*=12 Hz, 1H, H-3_{ax}), 1.72-1.77 (m, 2H, CH_2), 1.96 (brd, *J*=12 Hz, 1H, H-1_{eq}), 2.3-2.6 (m, 2H, H-4_{ax}, H-2_{eq}), 2.8-3.0 (m, 3H, H-7, H-6_{ax}), 3.38-3.46 (m, 1H, H-6_{eq}), 3.52 (brd, *J*=11 Hz, 1H, H-12b), 7.09 (td, *J*=7, 1 Hz, 1H, H-6_{ax}), 7.14 (td, *J*=7, 1 Hz, 1H, H-5), 7.48 (d, *J*=7 Hz, 1H, H-4), 7.93 (brs, NH), 9,65 (s, CHO); ^{13}C NMR 9.1 (CH_3), 22.0 (C-6), 26.3 (CH_2), 28.0 (C-3), 29.2 (C-1), 45.1 (C-5), 48.3 (C-2), 58.7 (C-12b), 61.5 (C-4), 108.7 (C-7a), 110.7 (C-11), 118.1 (C-8), 119.3 (C-9), 122.4 (C-10), 127.1 (C-7b), 134.6 (C-12a), 136.0 (C-11a), 203.1 (CHO); MS(EI) *m/z* (%) 282 (M^+, 35), 281 (M-1, 31), 253 (100), 225 (56), 197 (56), 184 (59), 169 (50), 168 (43), 149 (46), 144 (44). HRMS calcd for $C_{18}H_{22}N_2O$ 282.1732, found 282.1724

Acetalization of aldehydes 8. To a solution of crude **8** (0.59 g, 2.09 mmol) in acetic acid (10 ml) ethyleneglycol (0.58 ml) and freshly distilled $BF_3.Et_2O$ (1 ml) were added slowly. The mixture was stirred at room temperature for 15 min a brown solid appearing. The resulting suspension was poured into a mixture of aqueous Na_2CO_3 and CH_2Cl_2 in an ice bath. The organic layer was separated off, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic layers were washed with brine, dried and evaporated to give a dark foam, which was purified by chromatography (Al_2O_3). On elution from hexanes-CH_2Cl_2 (1:1) to CH_2Cl_2, 263 mg of a mixture of **10a**,**10b, and 10d** (6:1:0.5 ratio by ^1H NMR) and 26 mg of **10d** and **10c** (1:2 ratio) were isolated. Thus, the transformation of pure **5** to **10** was carried out in 33% overall yield. An analytical sample of **10a** was obtained by further chromatography (SiO_2, CH_2Cl_2).

(2*RS*,4*SR*,12b*SR*)-2-(1,3-Dioxolan-2-yl)-4-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (10a): TLC R_f = 0.40 (EtOAc:CH_2Cl_2 2:3); ^1H NMR (500 MHz, COSY) 0.93 (t, *J*=7.5 Hz, 3H, CH_3), 1.36 (q, *J*=12 Hz, 1H, H-1_{ax}), 1.48 (q, *J*=12 Hz, 1H, H-3_{ax}), 1.6-1.74 (m, 2H, CH_2), 1.76-1.84 (m, 2H, H-1_{eq} and H-2_{eq}), 2.14 (brd, *J*=12 Hz, 1H, H-3_{eq}), 2.32-2.42 (m, 2H, H-4_{ax} and H-6_{ax}), 2.74 (brd, *J*=12 Hz, 1H, H-7_{eq}), 2.86 (m, 1H, H-7_{ax}), 3.39-3.45 (brd, *J*=11 Hz, 2H, H-6_{eq} and H-12b), 3.82-4.0 (m, 4H, OCH_2), 4.63 (d, *J*=5.5 Hz, 1H, OCHO), 7.04 (td, *J*=7, 1 Hz, 1H, H-9), 7.08 (td, *J*=7, 1 Hz, 1H, H-10), 7.25 (dd, *J*=7, 1 Hz, 1H, H-11), 7.43 (dd, *J*=7,1 Hz, 1H, H-8), 7.92 (brs, 1H, NH); ^{13}C NMR(HMQC) 9.3 (CH_3), 21.9 (C-7), 26.4 (CH_2), 30.2 (C-3), 31.0 (C-1), 39.8 (C-2), 45.5 (C-6), 59.1 (C-12b), 61.8 (C-4), 64.9 and 65.0 (OCH_2), 106.8 (OCHO), 108.2 (C-7a), 110.7 (C-11), 118.1 (C-8), 119.2 (C-9), 121.2 (C-10), 127.2 (C-7a), 135.2 (C-12a), 136.0 (C-11a); MS(EI) *m/z* (%) 326 (M^+, 30), 325 (M-1, 43), 297 (100), 253 (22), 251 (20), 170 (21), 14 (18), 73 (16). HRMS calcd for $C_{20}H_{26}N_2O_2$ 326.1994, found 326.1983

(2*RS*,4*RS*,12b*RS*)-2-(1,3-Dioxolan-2-yl)-4-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (10b): ^1H NMR (significant signals) 0.99 (t, *J*=7.5 Hz, CH_3), 5.17 (d, *J*=7.5 Hz, OCHO);^{13}C NMR 9.3 (CH_3), 22.0 (C-7), 26.4 (CH_2), 29.8 (C-1), 29.6 (C-3), 33.4 (C-2), 45.6 (C-6), 55.1 (C-4), 58.1 (C-12b), 64.9 and 65.0 (OCH_2), 104.8 (OCHO), 108.2 (C-7a), 110.7 (C-11), 118.1 (C-8), 119.2 (C-9), 121.2 (C-10), 127.2 (C-7a), 135.2 (C-12a), 136.0 (C-11a)

(2*RS*,4*RS*,12b*SR*)- *and* (2*RS*,4*SR*,12b*RS*) 2-(1,3-Dioxolan-2-yl)-4-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*] quinolizine (10c and 10d): ^1H NMR (mixture of **10c** and **10d**) 0.89 (t, *J*=6.5 Hz, CH_3, **10d**), 0.90 (t, *J*=6.5 Hz, CH_3, **10c**), 1.10 -1.30 (m, 1H), 1.4-1.94 (m, 5H), 2.01-2.17 (m, 1H), 2.3-3.2 (m, 5H), 3.70 (dd, *J*=12, 3 Hz, H-12b, **10c**), 3.86-4.0 (m, 4H, OCH_2), 4.20 (br d, *J*=4 Hz, H-12b, **10d**), 4.63 (d, *J*=5.5 Hz, 1H, OCHO), 7.06 (td, *J*=7, 2 Hz, 1H, H-9), 7.15 (td, *J*=7, 2 Hz, 1H, H-10), 7.25 (d, *J*=8, 1H, H-11), 7.48 (d, *J*=7.5 Hz, 1H, H-8), 8.05 (brs, NH, **10d**); 8,19 (brs, NH, 10c); For **10c**: ^{13}C NMR 11.5 (CH_3), 16.9 (CH_2), 23.6 (C-7), 25.6 (C-3), 27.5 (C-1), 34.6 (C-2), 45.9 (C-6), 55.1 (C-12b), 58.2 (C-4), 64.9 (OCH_2), 107.3 (OCHO), 108.2 (C-7a), 111.1 (C-11), 118.8 (C-8), 119.1 (C-9), 121.8 (C-10), 127.5 (C-7a), 133.5 (C-12a), 136.0 (C-11a). For **10d**: ^{13}C NMR 9.2 (CH_3), 16.7 (C-7), 25.8 (CH_2), 28.2 (C-1), 31.3 (C-3), 36.1 (C-2), 47.0 (C-

6), 51.8 (C-12b), 55.2 (C-4), 64.9 (OCH_2), 106.9 (OCHO), 108.2 (C-7a), 111.0 (C-11), 117.9 (C-8), 119.3 (C-9), 121.2 (C-10), 127.5 (C-7a), 133.5 (C-12a), 135.9 (C-11a).

Cyclization in aqueous acetic acid of tetrahydropyridine 5. A solution of acetal **5** (1.2 g, 3.6 mmol) in 30% aqueous AcOH (200 ml) was heated at reflux for 16 h and then evaporated. After work-up as in the anhydrous method, a mixture of **8** and **9** (805 mg, 77% in a crude form) was isolated in a 3:1 ratio. The crude reaction was then submitted to acetalization as above and analyzed by glc/ms (see text). Owing to their similar mobilities, a mixture of **10a**, **10b**, **10d**, and **11a**, in which the first one is predominant (7:1:1:2, ratio by ^1H NMR), was collected on elution with CH_2Cl_2 (394 mg). Increasing the polarity to CH_2Cl_2-EtOAc (1:1), 74 mg of a mixture of **10d**, **10c**, and **11b** (1:2:2, ratio) was collected. Repeated purifications by chromatography on SiO_2 allowed the separation of compounds **10** from derivatives **11**. The overall yield for the transformation of tetrahydropyridine **5** to indoloquinolizine acetals **10** (see above for spectroscopic data) was 30%, being nearly 10% for the isolated by-products **11**.

(1*RS*,3*RS*,11b*RS*)-1[(1,3-Dioxolan-2-yl)methyl]-3-ethyl-1,2,3,5,6,11b-hexahydroindolizino[8,7-*b*]indole (11a): TLC R_f = 0.35 (EtOAc:CH_2Cl_2 2:3); ^1H NMR (500 MHz, COSY) 0.93 (t, *J*=7.5 Hz, CH_3), 1.34 and 1.86 (2m, 1H each, CH_2), 1.70-1.80 (m, 1H, H-2), 1.94-2.20 (m, 1H, H-2'), 2.03-2.08 (m, 1H, H-1), 2.82-3.00 (m, 2H, H-6), 3.28-3.46 (m, 2H, H-5), 3.83-3.97 (m, 4H, OCH_2), 3.97 (d, *J*=6Hz,1 H, H-11b), 4.07 (m, 1H, H-3), 5.07 (t, *J*=5 Hz, 1H, OCHO), 7.04 (td, *J*=7 Hz, 1H, H-8), 7.09 (td, *J*=7 Hz, 1H, H-9), 7.27 (d, *J*=7 Hz, 1H, H-10), 7.42 (d *J*=7 Hz, H-7), 9.1 (brs, 1H, NH); ^{13}C NMR (HMQC): 10.5 (CH_3), 22.3 (C-6), 25.6 (CH_2), 34.4 (C-1), 38.5 (C-2), 39.5 (CH_2-OCHO), 46.7 (C-5), 63.4 (C-11b), 64.9 and 65.1 (OCH_2), 67.5 (C-3), 103.4 (OCHO), 108.0 (C-6a), 110.8 (C-10), 118.0 (C-7), 119.0 (C-8), 120.8 (C-9), 127.0 (C-6b), 135.5 (C-11a), 135.6 (C-10a); MS(EI) *m/z* (%) 326 (M^+, 39), 325 (M-1, 42), 297 (100), 281 (10), 251 (27), 212 (65), 197 (73), 171 (20), 169 (22), 156 (21), 144 (18), 73 (21).

(1*RS*,3*RS*,11b*SR*)-1[(1,3-Dioxolan-2-yl)methyl]-3-ethyl-1,2,3,5,6,11b-hexahydroindolizino[8,7-*b*]indole (11b): ^1H NMR (500 MHz, COSY) 0.91 (t, *J*=7.5 Hz, CH_3), 1.19-1.39 (m, 2H, $CH_ACH_BCH_3$ and H-2), 1.8-1.9 (m, 1H, $CH_ACH_BCH_3$), 1.95-2.10 (m, 2H, CH_2-OCHO), 2.19-2.24 (m, 1H, H-2), 2.28-2.34 (m, 1H, H-1), 2.55 (brd, *J*=11.5 Hz, 1H, H-6), 2.71-2.80 (m, 1H, H-6), 2.80-3.00 (m, 1H, H-3), 3.05-3.12 (m, 1H, H-5), 3.38-3.45 (m, 1H, H-5), 3.82-4.07 (m, 4H, OCH_2), 4.47 (brs, 1H, H-11b), 5.14 (t, *J*=5.5 Hz, 1H, OCHO), 7.06 (td, *J*=8, 1 Hz, 1H, H-8), 7.09 (td, *J*=8, 1 Hz, 1H, H-9), 7,28 (d, *J*=8 Hz, 1H, H-10), 7.44 (d *J*=8 Hz, H-7), 8.8 (brs, 1H, NH);^{13}C NMR (HMQC) 10.6 (CH_3), 15.9 (C-6), 25.7 (CH_2), 38.2 (C-1), 39.2 (C-2), 39.9 (CH_2-OCHO), 42.5 (C-5), 58.3 (C-3), 62.5 (C-11b), 64.7 and 64.9 (OCH_2), 104.3 (OCHO), 107.0 (C-6a), 110.7 (C-10), 117.9 (C-8), 119.0 (C-9), 121.2 (C-10), 127.5 (C-6b), 135.8 (C-11a), 136.0 (C-10a); MS(EI) *m/z* (%) 326 (M^+,54), 325 (M-1,51), 298 (19), 297 (100), 253 (14), 251 (13), 212 (89), 197 (93), 171 (22), 169 (24), 156 (19), 144 (21), 73 (36).

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3. There are no precedents for the synthesis of 2,4-dialkylsubstituted octahydroindolo[2,3-*a*]quinolizines. The preparation of 2-oxo-4-alkyl derivatives in this series using an imino Diels-Alder process has been

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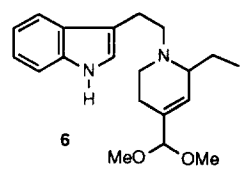
7. In this process a minor amount of isomeric tetrahydropyridine **6** (~3% yield), resulting from an isomerization of the dihydropyridinium salt intermediate, was isolated. TLC R_f = 0.25 (EtOAc:CH_2Cl_2 2:3); ^{1}H NMR (500 MHz) 0.91 (t, 3H, CH_3), 1.55-2.09 (m, 4H, H-5, CH_2CH_3), 2.9-3.05 (m, 4H, CH_2), 3.05-3.35 (m, 3H, H-2 and H-6), 3.28 and 3.29 (2s, 3H each, OCH_3), 4.55 (s, 1H, OCHO), 5.77 (s, 1H, H-3), 7.03 (d, *J*=2 Hz, 1H, H-2), 7.12 (td, *J*=7 Hz, 1H, H-2), 7.16 (td, *J*=7 Hz, 1H, H-6), 7.34 (d, *J*=7 Hz, 1H, H-7), 7.60 (d, *J*=7 Hz, 1H, H-4), 8.05 (brs, 1H, N-H); ^{13}C NMR 10.0 (CH_3), 22.9 (C-5), 23.1 (CH_2), 26.0 (CH_2CH_3), 47.0 (C-6), 53.0 (OCH_3), 54.6 (CH_2N), 60.0 (C-2), 105.1 (OCHO), 111.1 (C-7), 114.5 (C-3'), 118.8 (C-4'), 119.1 (C-5'), 121.6 (C-2'), 122.0 (C-2), 127.5 (C-3a), 128.0 (C-3), 133.5 (C-4), 136.2 (C-7a).



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16. Tryptophyl bromide was synthesized from the corresponding alcohol in 98% yield (CBr_4, PPh_3, CH_2Cl_2, 0 °C).

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